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(71) Applicant:
SANKYO COMPANY LIMITED
Chuo-ku, Tokyo 103-0023 (JP)

(72) Inventors:
- **TSUJITA, Yoshio,**
  Sankyo Company, Limited
  Toyko 140 (JP)
- **FUJIWARA, Toshihiko,**
  Sankyo Company, Limited
  Toyko 140 (JP)
- **SADA, Toshio,**
  Sankyo Company, Limited
  Toyko 140 (JP)
- **MAEDA, Naoyuki,**
  Sankyo Company, Limited
  Toyko 140 (JP)

(74) Representative:
Gibson, Christian John Robert
MARKS & CLERK,
57/60 Lincoln's Inn Fields
London WC2A 3LS (GB)

(54) MEDICINAL COMPOSITIONS

(57) A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents exhibits excellent arteriosclerotic progress inhibitory effects, and is useful as a drug, particularly as a drug for the prevention or treatment of arteriosclerosis.

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Description

[Technical Field of the Invention]

[0001] The present invention relates to a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), and a method which comprises administering in combination effective amounts of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for preventing or treating diseases (particularly arteriosclerosis).

[Background of the Invention]

[0002] The occurrence of atherosclerosis is increasing with the adoption of Western-style diet and the growth of the aged population. This disease is the main cause of such disorders as myocardial infarction, cerebral infarction and cerebral apoplexy, and there is a need for its effective prevention and treatment. Examples of risk factors which cause atherosclerosis include hyperlipemia (particularly hypercholesterolemia), hypertension and saccharometabolism disorders based on insulin resistance. In addition, there are many cases in which these risk factors occur in the form of complications (Syndrome X), and are considered to be mutually interrelated [Diabetes, 37, 1595-1607 (1988)].

[0003] Efforts have been made for the purpose of preventing and treating atherosclerosis by suppression of various risk factors such as hyperlipemia, hypertension and insulin resistance. Although HMG-CoA reductase inhibitors like pravastatin improve hyperlipemia, their inhibitory activity on arteriosclerosis in a case of administration alone is not enough [Biochim. Biophys. Acta, 960, 294-302 (1988)]. In addition, even insulin resistance improving agents like troglitazone do not exhibit sufficient atherosclerosis inhibitory activity in a case of administration alone (Japanese Patent Application (Kokai) No. Hei 7-41423).

[0004] On the other hand, among drugs for the treatment of hypertension, it has been reported that atherosclerotic lesions are suppressed when angiotensin converting enzyme (ACE) inhibitors that inhibit the renin-angiotensin system [Hypertension, 15, 327-331 (1990)] or angiotensin II receptor antagonists [Jpn. Circ. J., 60 (Suppl. I), 332 (1996)] are administered to animals having normal blood pressure and hypercholesterolemia. Angiotensin II not only exhibits vasoconstrictive activity, but also activity that stimulates the production of growth factors such as PDGF [Hypertension, 13, 706-711 (1989)] and activity that stimulates migration of neutrophils and macrophages [Eur. Heart J., 11, 100-107 (1990)]. Although the mechanism in which renin-angiotensin system inhibitors suppress atherosclerosis is not clear at the present time, there is a possibility that the mechanism for suppressing atherosclerosis may be a function at the site of the lesion which is different from their blood pressure lowering action. However, since inhibitors of renin-angiotensin system are unable to lower serum lipids [J. Cardiovasc. Pharmacol., 15, S65-S72 (1990)], their administration alone has limitations on the treatment of arteriosclerosis.

[0005] In addition, although troglitazone, glibenclamide and captopril are administered concomitantly to diabetes patients, there is no suggestion indicated whatsoever relating to the prevention and treatment of arteriosclerosis [J. Clinical Therapeutic & Medicines, 9 (Supp. 3), 39-60 (1993)].

[Disclosure of the Invention]

[0006] As a result of earnestly conducting various research in consideration of the importance of the prevention and treatment of arteriosclerosis, the inventors of the present invention found a method to solve the above-mentioned problems involved in the prior art and to obtain a preventive and/or therapeutic effect on arteriosclerosis by using the combination of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of one or more of insulin resistance improving agents.

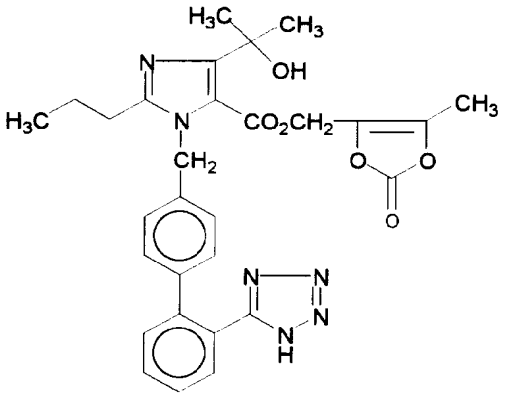
[0007] The present invention provides a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), a method which comprises administering in combination effective amounts of one or more drugs selected

from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for prevention or treatment of diseases (particularly arteriosclerosis), or a pharmaceutical composition for administering at the same time or at the different time one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis).

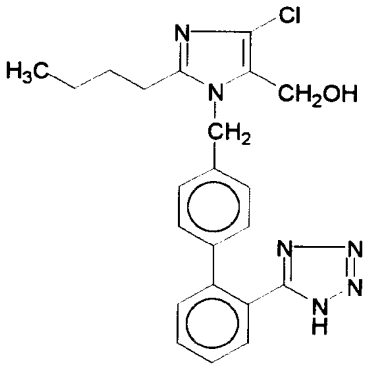
[0008] The active ingredients of the pharmaceutical composition of the present invention (particularly a pharmaceutical composition for the prevention or treatment of arteriosclerosis), or the active ingredients of a method for preventing or treating diseases (particularly arteriosclerosis) include one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

[0009] Representative examples of angiotensin II receptor antagonists as an active ingredient of the present invention include biphenyltetrazole compounds and biphenylcarboxylic acid compounds described in Japanese Patent Application (Kokai) No. Hei 5-78328, Japanese Patent Application (Kokai) No. Sho 63-23868, Japanese Patent Application (Kokai) No. Hei 4-364171, Japanese Patent Application (Kokai) No. Hei 4-159718 or Japanese PCT Application (Kokai) No. Hei 4-506222, preferably biphenyltetrazole compounds, more preferably CS-866, losartan, candesartan, valsartan or irbesartan, still more preferably CS-866, losartan or candesartan, and most preferably CS-866.

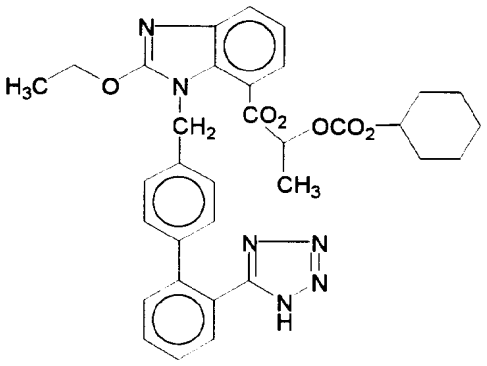
[0010] The following indicates the chemical planar structural formulae of some typical examples of angiotensin II receptor antagonists.



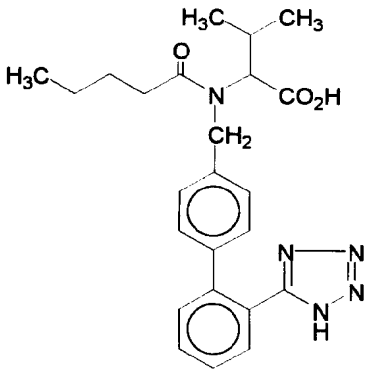
CS-866



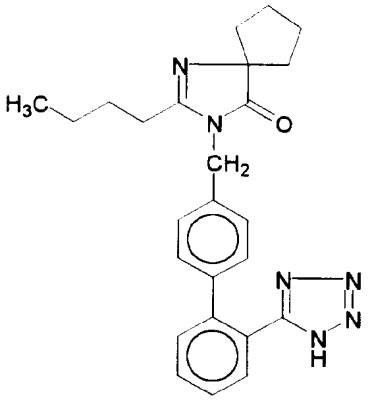
Losartan



Candesartan



Valsartan



Irbesartan

[0011] CS-866 is described in Japanese Patent Application No. (Kokai) No. Hei 5-78328 and the like, and its chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. The CS-866 of the present application includes its carboxylic acid derivative, phar-

macologically acceptable esters of its carboxylic acid derivative (such as CS-866) and their pharmacologically acceptable salts.

[0012] Losartan (DUP-753) is described in Japanese Patent Application (Kokai) No. Sho 63-23868, U.S. Patent No. 5,138,069 and the like, and its chemical name is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazole-5-methanol. The losartan of the present application includes its pharmacologically acceptable salts (such as losartan potassium salt).

[0013] Candesartan (TCV-116) is described in Japanese Patent Application (Kokai) No. Hei 4-364171, EP-459136, U.S. Patent No. 5,354,766 and the like, and its chemical name is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate. The candesartan of the present application includes its carboxylic acid derivative, pharmacologically acceptable esters of its carboxylic acid derivative (such as TCV-116) and their pharmacologically acceptable salts.

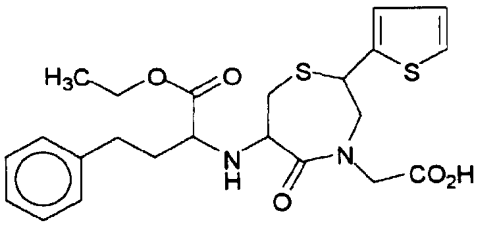
[0014] Valsartan (CGP-48933) is described in Japanese Patent Application (Kokai) No. Hei 4-159718, EP-433983 and the like, and its chemical name is (S)-N-valeryl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)valine. The valsartan of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0015] Irbesartan (SR-47436) is described in Japanese PCT Application (Kokai) No. Hei 4-506222, WO91-14679 and the like, and its chemical name is 2-N-butyl-4-spirocyclopentane-1-[2'-(tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazolin-5-one. The irbesartan of the present application includes its pharmacologically acceptable salts.

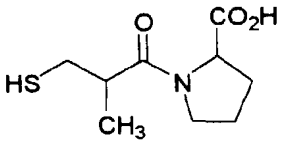
[0016] In addition, where the above-mentioned compounds have asymmetric carbons, the angiotensin II receptor antagonists of the present invention also include optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included.

[0017] Representative examples of the angiotensin converting enzyme inhibitors as an active ingredient of the present invention include tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds described in Japanese Patent Application (Kokai) No. Sho 61-267579, Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,374,829, Japanese Patent Application (Kokai) No. Sho 58-126851, Japanese Patent Application (Kokai) No. Sho 58-206591, Japanese Patent Application (Kokai) No. Sho 57-77651, Japanese Patent Application (Kokai) No. Sho 55-9058, Japanese Patent Application (Kokai) No. Sho 58-203971 and Japanese Patent Application (Kokai) No. Sho 63-258459, preferably temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril or quinapril, more preferably temocapril, captopril or enalapril, and most preferably temocapril.

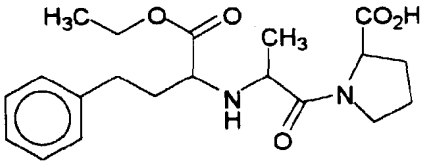
[0018] The following indicates the chemical planar structural formulae of some typical examples of angiotensin converting enzyme inhibitors.



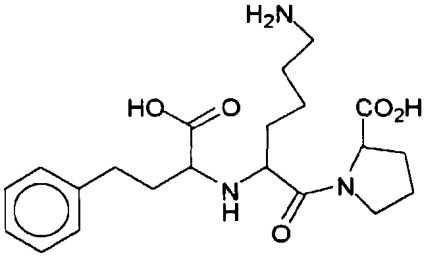
Temocapril



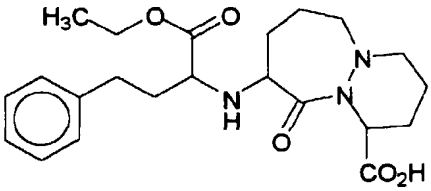
Captopril



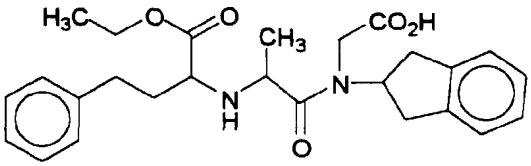
Enalapril



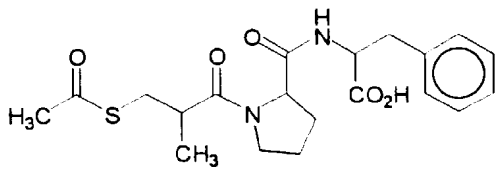
Lisinopril



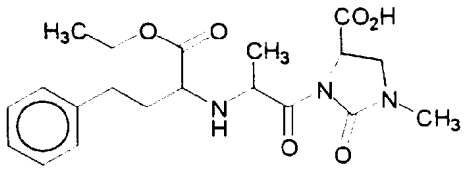
Cilazapril



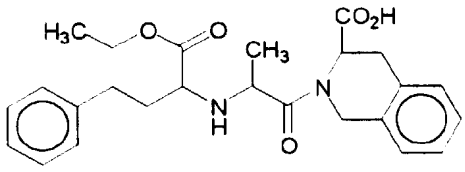
Delapril



Alacepril



Imidapril



Quinapril

[0019] Temocapril is described in Japanese Patent Application (Kokai) No. Sho 61-267579, U.S. Patent No. 4,699,905 and the like, and its chemical name is (+)-(2S,6R)-[6-(1S)-1-ethoxycarbonyl-3-phenylpropylamino]-5-oxo-2-(2-thienyl)perhydro-1,4-thiazepin-4-yl acetic acid. The temocapril of the present application includes its dicarboxylic acid derivatives, its pharmacologically acceptable salts, its pharmacologically acceptable monoesters and its pharmacologically acceptable salts (such as temocapril hydrochloride).

[0020] Captopril is described in Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,046,889 and the like, and its chemical name is 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. The captopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0021] Enalapril is described in U.S. Patent No. 4,374,829 and the like, and its chemical name is N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline. The enalapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts (such as enalapril maleate).

[0022] Lisinopril is described in Japanese Patent Application (Kokai) No. Sho 58-126851, U.S. Patent No. 4,555,502 and the like, and its chemical name is (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline. The lisinopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0023] Cilazapril is described in Japanese Patent Application (Kokai) No. Sho 58-206591, U.S. Patent No. 4,512,924 and the like, and its chemical name is (1S,9S)-9-[(S)-1-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazino[1,2-α][1,2]diazepine-1-carboxylic acid. The cilazapril of the present application includes its pharmacologically acceptable esters and pharmacologically acceptable salts.

[0024] Delapril is described in Japanese Patent Application (Kokai) No. Sho 57-77651, U.S. Patent No. 4,385,051 and the like, and its chemical name is (S)-N-(2,3-dihydro-1H-inden-2-yl)-N-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]glycine. The delapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0025] Alacepril is described in Japanese Patent Application (Kokai) No. Sho 55-9058, U.S. Patent No. 4,248,883 and the like, and its chemical name is 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine. The alacepril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0026] Imidapril is described in Japanese Patent Application (Kokai) No. Sho 58-203971, U.S. Patent No. 4,508,727 and the like, and its chemical name is (4S)-3-[(2S)-2-[(1S)-1-ethoxycarbonyl-3-phenylpropylamino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid. The imidapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

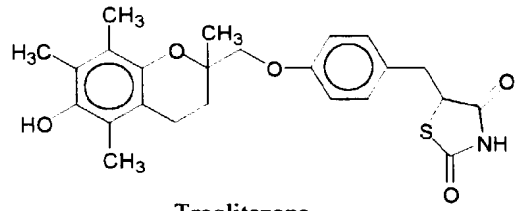
[0027] Quinapril is described in Japanese Patent Application (Kokai) No. Sho 63-258459, U.S. Patent No. 4,761,479 and the like, and its chemical name is (S)-2-[(2S)-2-(1S)-1-ethoxycarbonyl-3-phenylpropylamino)propionyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid. The quinapril of the present application includes its pharmacologically accepta-

ble esters and its pharmacologically acceptable salts.

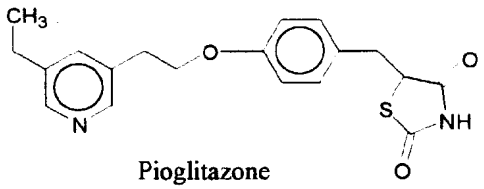
[0028] Where the above-mentioned angiotensin converting enzyme inhibitors of the present invention have asymmetric carbons, said angiotensin converting enzyme inhibitors of the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0029] The insulin resistance improving agents as another active ingredient of the present invention are inherently used for the prevention and treatment of diabetes. Representative examples include thiazolidinedione compounds, oxazolidinedione compounds or oxadiazolidinedione compounds described in Japanese Patent Application (Kokai) No. Hei 4-69383, WO 89/08651, WO 91/07107, WO 92/02520, WO 94/01433, USP-4287200, USP-4340605, USP-4438141, USP-4444779, USP-4461902, USP-4572912, USP-4687777, USP-4703052, USP-4725610, USP-4873255, USP-4897393, USP-4897405, USP-4918091, USP-4948900, USP-5002953, USP-5061717, USP-5120754, USP-5132317, USP-5194443, USP-5223522, USP-5232925 and USP-5260445, preferably thiazolidinedione compounds, more preferably troglitazone, pioglitazone, englitazone or BRL-49653, still more preferably troglitazone or pioglitazone, and most preferably troglitazone.

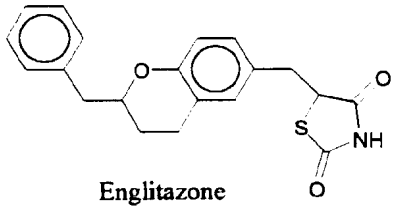
[0030] The following indicates the chemical planar structural formulae of some typical examples of insulin resistance improving agents.



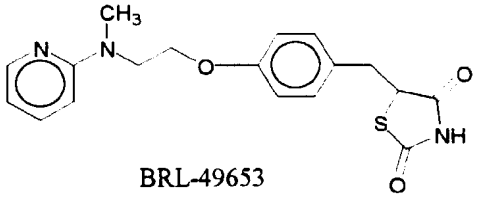
Troglitazone



Pioglitazone



Englitazone



BRL-49653

[0031] Troglitazone is described in Japanese Patent Application (Kokai) No. Sho 60-51189, U.S. Patent No. 4,572,912 and the like, and its chemical name is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione. The troglitazone of the present application includes its pharmacologically acceptable salts.

[0032] Pioglitazone is described in Japanese Patent Application (Kokai) No. Sho 55-22636, U.S. Patent No. 4,287,200 and the like, and its chemical name is 5-[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenylmethyl]-2,4-thiazolidinedione. The pioglitazone of the present application includes its pharmacologically acceptable salts.

[0033] Englitazone is described in Japanese Patent Application (Kokai) No. Sho 61-271287, U.S. Patent No. 4,703,052 and the like, and its chemical name is 5-(3,4-dihydro-2-benzyl-2H-benzopyran-6-ylmethyl)-2,4-thiazolidinedione. The englitazone of the present application includes its pharmacologically acceptable salts.

[0034] BRL-49653 is described in Japanese Patent Application (Kokai) No. Hei 1-131169, U.S. Patent No. 5,002,953 and the like, and its chemical name is 5-[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenylmethyl]-2,4-thiazolidinedione. The BRL-49653 of the present application includes its pharmacologically acceptable salts.

[0035] Where the above-mentioned insulin resistance improving agents of the present invention have asymmetric carbons, said resistance improving agents the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0036] In the present invention, one or more drugs are selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors (preferably the group consisting of angiotensin II receptor antagonists), and one or more insulin resistance improving agents are selected; and preferably the one drug is selected from angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and the other drug is selected

from insulin resistance improving agents to use in combination.

[0037] Preferable examples of the pharmaceutical composition of the present invention are as follows:

(1) a pharmaceutical composition wherein as active ingredients, the angiotensin II receptor antagonists are chosen from biphenyltetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds;
(2) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril;
(3) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril;
(4) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril;
(5) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan;
(6) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866;
(7) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists;
(8) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan;
(9) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from angiotensin converting enzyme inhibitors;
(10) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is temocapril;
(11) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds;
(12) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(13) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone; and,
(14) a pharmaceutical composition wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

In addition, a pharmaceutical composition obtained by selecting as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors from the group (1) to (10), by selecting as active ingredients, insulin resistance improving agents from the group (11) to (14) and by combining these groups in an arbitrary manner is also preferable, examples of which are as follows:
(15) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(16) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(17) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;
(18) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglita-

zone;

(19) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(20) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agent is troglitazone;

(21) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agent is troglitazone; and,

(22) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and as the other active ingredient, the insulin resistance improving agent is troglitazone.

[Effect of the Invention]

[0038] A drug comprising one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents, which are the active ingredients of the pharmaceutical composition of the present invention (particularly a composition for prevention or treatment of arteriosclerosis), has excellent inhibitory action on aortosclerosis and excellent inhibitory action against onset of xanthochromia occurring in limb joints, and low toxicity. Consequently, it is useful as a drug for the prevention and treatment (particularly for treatment) of arteriosclerosis or xanthochromia.

[0039] According to the present invention, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and insulin resistance improving agents exhibit excellent effects by using two of these agents in combination as compared with being used alone. In addition, these effects can be achieved without requiring that both types of agents be present in the body simultaneously.

[0040] Namely, such effects can be obtained even if both types of agents do not simultaneously have certain concentrations in the blood. According to hypothesis, if two types of agents used in the present invention are both incorporated in vivo and reach the receptors, they have the effect of turning on a switch in vivo. Thus, even if it appears that such effects are not demonstrated at their blood concentrations in course of time after their administration, the switch is actually still on, thereby allowing demonstration of preventive or therapeutic effects on arterial sclerosis possessed by the one type of substance. When the other type of agent is administered in this state, in addition to the preventive or therapeutic effects on arterial sclerosis possessed by that agent, the effects of the drug initially administered are combined to obtain excellent effects. Naturally, since it is convenient clinically to administer two types of agents simultaneously, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and an insulin resistance improving agent can be administered in the form of a combination drug. In cases where it is undesirable to physically mix both agents simultaneously in consideration of pharmaceutical formulation technology, each individual agent may be administered simultaneously. In addition, as was stated above, since excellent effects are demonstrated even if the two types of agents are not administered simultaneously, each individual agent can also be administered at a suitable interval in succession. The maximum administration interval of the two types of agents to demonstrate the excellent effects brought about by said two types of agents can be determined by clinical or animal studies.

[Industrial Applicability]

[0041] The administration route of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention is typically the oral administration route. Thus, the two types of agents can either be prepared in the form of two separate administrations or in the form of a single administration by physically mixing the two types of agents. The administration form can be, for example, a powder, granules, tablet or capsule and the like, and can be prepared by using conventional pharmaceutical formulation techniques.

[0042] The dose and administration ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention can be changed over a wide range according to various conditions such as the individual activity of each agent, the patient's symptoms, age and body weight, and the like. For example, in the case of insulin resistance improving agents, since the in vivo activities of troglitazone and BRL-49653 by using a diabetic animal model are different, the dose of these two agents may be different by a factor of ten or more. In addition, for both agents consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and insulin resistance improving agents, their doses in the case used for prevention or treatment of arteriosclerosis in the present invention can be lower than their dose for use

as hypotensive agents and diabetes therapeutic agents respectively, which are their well-known applications. In addition, their doses can be made even lower due to the excellent effects resulting from combined use of both types of agents. For example, in the case of using CS-866 and troglitazone for the object of the present invention, their doses are lower than the approximately 5 to 100 mg and approximately 10 to 2000 mg, respectively, which are the doses for adults (mg/day) for use as a hypotensive agent and diabetes therapeutic agent in their well-known applications, being able to be approximately 1 to 80 mg and approximately 1 to 1000 mg, respectively.

[0043] As has been described above, the doses of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of the insulin resistance improving agents can be varied over a wide range, in general, and their doses for adults (mg/day) are approximately 0.5 to 100 mg and approximately 0.05 to 1,500 mg, respectively.

[0044] The ratio of the doses of these two types of agents can also be varied over a wide range, in general, and the dose ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to the insulin resistance improving agents can be, in terms of weight ratio, within the range from 1:200 to 200:1.

[0045] In the present invention, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and the insulin resistance improving agents are administered at the respective doses described above once a day or divided among several times per day, and may be administered simultaneously or separately at respectively different times.

[Best Mode for Carrying Out the Invention]

[0046] The present invention will be described more specifically by way of Examples and Preparation examples, but the scope of the present invention is not limited to them.

(Example 1)

Arterial sclerosis Progress Inhibitory Effect

[0047] A certain amount of an agent was administered orally for 32 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: supra (Biochimica et Biophysica Acta), etc.] in groups of 4 to 7 animals each. Incidentally, food consumption was restricted to 120 g/day per animal. Blood samples were collected immediately before administration of the agent and 4, 8, 12, 16, 20, 24, 28 and 32 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. The test animals were subjected to autopsy in the 32nd week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints (%). Those results are shown in Tables 1 and 2.

[Table 1]

Surface Area of Aortic Lesions											
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)							
				Arcuate region		Thoracic part		Abdominal region		Overall	
1	CS-866 + Troglitazone	1 + 25	5	52	10	9	3	13	2	21	4
	CS-866	1	6	68	10	26	8	19	5	34	7
	Troglitazone	25	7	80	7	57	12	32	8	54	9
	Control	-	7	83	6	59	7	39	4	56	4

[Table 2]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
1	CS-866 + Troglitazone	1 + 25	4	75	63	69
	CS-866	1	6	100	100	100
	Troglitazone	25	7	93	86	89
	Control	-	7	100	100	100

(Example 2)

Arterial sclerosis Progress Inhibitory Effect

[0048] A certain amount of an agent was administered orally for 31 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: described supra (Biochimica et Biophysica Acta), etc.] in groups of 5 to 7 animals each. Incidentally, food consumption was restricted to 100 g/day per animal. Blood samples were collected immediately before administration of the agent and 8, 16, 24 and 31 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. In addition, the test animals were subjected to autopsy in the 31st week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints. Those results are shown in Tables 3 and 4.

[Table 3]

Surface Area of Aortic Lesions							
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
2	CS-866 + pioglitazone	0.5 + 20	6	62±8	29±10	24±6	36±7
3	CS-866 + BRL-49653	0.5 + 2.5	5	52±5	32±7	25±5	34±5
	CS-866	0.5	7	66±5	41±10	32±8	44±7
	Pioglitazone	20	7	65±6	62±12	32±6	52±8
	BRL-49653	2.5	6	83±2	54±12	29±4	52±5
	Control	-	7	84±5	59±9	32±11	54±8

[Table 4]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
4	Candesartan + troglitazone	1 + 25	7	86	86	86
	Candesartan	1	7	100	100	100
	Troglitazone	25	7	100	86	93
	Control	-	7	100	100	100

(Formulation Example 1)

[0049]

Tablets	
CS-866	4.0 mg
Troglitazone	100.0
Lactose	244.0
Cornstarch	50.0
Magnesium stearate	2.0
	400 mg

[0050] The above-mentioned prescriptions are mixed and formed into tablets with a tablet-making machine to obtain tablets containing 400 mg per tablet.

[0051] These tablets can be provided with a sugar-coating if necessary.

Claims

1. A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

2. A pharmaceutical composition according to Claim 1 wherein the angiotensin II receptor antagonists are biphenyl tetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

3. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.

4. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

5. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.

6. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from chosen from CS-866, losartan and candesartan.

7. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866.

8. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists.

9. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.

10. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin converting enzyme inhibitors.

11. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril.

12. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

13. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

14. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

15. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

16. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

17. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

18. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

19. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

20. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

21. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.

22. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866, and the insulin resistance improving agent is troglitazone.

23. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and the insulin resistance improving agent is troglitazone.

24. A pharmaceutical composition according to Claims 1 to 23, wherein said pharmaceutical composition is a composition for preventing or treating arteriosclerosis.

25. The use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of one or more insulin resistance improving agents for preparing a pharmaceutical composition.

26. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

27. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

28. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

29. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

30. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

31. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.

32. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agent is troglitazone.

33. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril and the insulin resistance improving agent is troglitazone.

34. The use according to Claims 25 to 33, wherein the pharmaceutical composition is a composition for preventing or treating arteriosclerosis.

35. A method for preventing or treating arteriosclerosis which comprises administering in combiniation an effective amount of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to a warm blooded animal.

36. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

37. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

38. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

39. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

40. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

41. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent administered in combination is troglitazone.

42. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agent administered in combination is troglitazone.

43. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is temocapril and the insulin resistance improving agent administered in combination is troglitazone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02407

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K45/06, A61K31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K45/06, A61K31/33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Toru Murakami, Nobuhiro Yamada "Can ACE inhibitors prevent arteriosclerosis? (in Japanese)", Strides of Medicine, (1995), Vol. 174, No. 10. p. 810-813	1 - 34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
October 1, 1997 (01. 10. 97)	October 21, 1997 (21. 10. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 35 - 43
because they relate to subject matter not required to be searched by this Authority, namely:
Inventions of Claims 35 to 43 pertain to methods for treatment of the human or animal body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)